

## **Prevalence and risk factors for atrial fibrillation and stroke among elderly patients hospitalized in a rehabilitation center.**

**Ju-fei Wang<sup>1</sup>, Ming-jun Feng<sup>1</sup>, Xiao-min Chen<sup>1</sup>, Hui-min Chu<sup>2\*</sup>**

<sup>1</sup>Department of Cardiology, Fenghua Hospital, 36 Park Road, Fenghua, PR China

<sup>2</sup>Department of Cardiology, Ningbo No.1 Hospital Affiliated to Zhejiang University, Haishu District, Ningbo, PR China

### **Abstract**

**The purpose of this study was to investigate the prevalence and risk factors of Atrial Fibrillation (AF) and stroke in elderly patients hospitalized in a rehabilitation center. Multivariable logistic regression was performed to assess the association between AF (or stroke) and age, gender, hypertension, diabetes, Chronic Obstructive Pulmonary Disease (COPD), Chronic Heart Failure (CHF), Left Atrium (LA) diameter, warfarin treatment, alcohol consumption, liver dysfunction, smoking and other factors. In this retrospective study, a total of 587 subjects were enrolled from one rehabilitation center (59% men, mean age 76.6 years), with long-term bedridden patients comprising a majority of the sample population (84.8%). During the 3-year study, 54 cases of AF (9.2%) and 49 cases of stroke (8.3%) were documented. Gender was not associated the incidence of AF, although female patients had a significantly higher incidence of stroke (P=0.003). Our results show that age, hypertension, diabetes, COPD, LA diameter and CHF were associated with AF (P<0.05). Age, AF, hyperlipidemia, hypertension, heart disease, smoking, and treatment with warfarin or statins were associated with stroke (P<0.05). Age, hypertension and CHF were independent risk factors of AF, whereas hypertension and AF were independent predictors of stroke in this cohort. Our data suggest the necessity for a geriatric rehabilitative approach that implements comprehensive strategies for both disease managements and preventions of AF and stroke.**

**Keywords:** Atrial fibrillation, Stroke, Elderlypatients, Rehabilitation center.

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### **Introduction**

Stroke happens when blood supply is interrupted or when blood leaks from blood vessels leading to damage in brain. Each year, twenty million individuals all over the world suffer from strokes. This makes it one of the most rapid and rising causes of morbidity as well as mortality. Strokes are a predisposition for epilepsy, fall, as well as depression and are a primary cause of functional impairment, with 20% of the survivors needing institutionalized care post three months and around fifteen to thirty percent ending up with a permanent disability. Strokes are not regarded as a condition which impacts the developed nations anymore. Worldwide, 12.6 mil individuals are suffering from moderate to severe disability post strokes and among them, 8.9 mil individuals belong to low as well as middle-income nations [1]. Low as well as middle income nations in the Asia-Pacific area make up for around 85.5 percentage of the stroke-related deaths all over the world, and the number of disability-adjusted lifetime in those nations is nearly seven times that seen in high income nations. In India alone, it is predicted that around 6.36 mil disability-adjusted lifetime is lost due to strokes [2]. China as well as India have the biggest population and make up for the highest statistics in stroke-related deaths. The vast presence of strokes [3] in India

is observed as 99 to 222 per 100,000, individuals with around 1.44 to 1.64 mil cases of novel strokes diagnosed each year. Moreover, research has shown that the average age of individuals afflicted with strokes in developing nations is fifteen years lesser than that is developed nations.

AF refers to an independent risk factor for strokes [3,4], as well as consequent deaths as well as disabilities. AF independently heightens the risk of strokes five-fold in an age-dependent way. AF impacts 5% of the population above the age of seventy, and its presence reaches nearly 10% for people above eighty. It is anticipated that AF will rise in the near future due to the ageing of the population. Adjusted-dose warfarin for achieving an International Normalized Ratio (INR) between two and three is confirmed to considerably decrease the risk of strokes related to AF [5]. Birmingham AF treatment of aged, prospective, randomized, open label trial, contrasted the efficiency of warfarin (INR 2-3) with aspirin 75 mg every day, for preventing strokes in AF individuals with no previous cases of strokes, over the age of seventy-five. The primary end point was severe or fatal disabling strokes, intracranial haemorrhage, or clinically considerably systematic arterial embolism. The trial proved the superiority of warfarin over aspirin to prevent strokes in a population of older AF

patients. The frequency of ischemic strokes, systematic arterial embolisms as well as haemorrhagic strokes was fifty-two percent lesser in the anti-coagulated patients. The warfarin vs. aspirin for preventing strokes in octogenarians with AF trials particularly addressing the efficiency of modified doses of Warfarin (INR 2-3) vs. 300 mg of aspirin in patients aged from eighty to ninety. Primary endpoint was combined death, thrombo-embolism, major bleeding as well as withdrawal from designated treatment. The presence as well as risk factor for AF as well as strokes amongst older patients hospitalized in a rehabilitation centre.

## Methods

This retrospective case-controlled study was conducted at the Ningbo inpatient rehabilitation center, located in Ningbo, an east coast city of China. The volume of this centre is 120 beds.

**Inclusion and exclusion criteria:** The elder aged  $\geq 65$  (65-86), who were admitted between January 2010 and May 2013 were eligible for the study (622 individuals). Actually, 587 patients were enrolled in this study. Patients who were admitted and discharged on the same day were excluded (N=35). Eligibility information was obtained from the electronic database in this rehabilitation center, and patient data were extracted and screened for the inclusion criteria. Research was conducted in a compliance with the Department of Cardiology, Ningbo No.1 Hospital Affiliated to medical College of University institutional review board, and the approval was obtained prior to data extraction.

**Subjects and clinical presentation:** Of these 587 patients enrolled in the 3-year study, 344 (59%) were male and 243 (41%) were female. The average age was  $76.6 \pm 9.3$  years old, and 498 subjects (84.8%) were long-term bedridden patients. The study was divided into AF and stroke data sets based on the clinical presentation of patients at admission. Patients in Group 1 (AF group; N=54) and Group 2 (non-AF group; N=533) were analyzed for the prevalence and risk factors of AF. Patients in Group 3 (stroke group; N=49) and Group 4 (non-stroke group; N=538) were analyzed for the prevalence and risk factors of stroke.

The Maximal Heart Rates (MHR) of patients in the study were recorded. AF was identified by analysis of episodes recorded during Holter Monitoring (HM; 24 hour) or by ElectroCardioGram (ECG), in accordance with international guidelines. Paroxysmal AF (PAF) was defined as two different episodes of AF that relief spontaneously in less than 7 days (usually within 48 hours), and were mostly self-limiting. Persistent AF was defined as an episode lasting longer than 7 days, which usually required treatments (drug or electrical cardioversion) to cease. The LA diameter, Left Ventricular Ejection Fraction (LVEF), and Left Ventricular End-Diastolic Dimension (LEVDD) were measured by ECG. CHF presented as symptomatic (New York Heart Association [NYHA] classes III-IV) and systolic (LVEF  $<40\%$ ) heart failure. Patient manifestations of organic heart disease (coronary artery disease, valvular heart disease, cardiomyopathy, myocarditis,

hypertensive heart disease, pulmonary heart disease, sick sinus syndrome, and high grade atrioventricular block), liver dysfunction (greater than 2-fold increase above the upper limit of bilirubin, or a 3-fold increase beyond the upper range of aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase levels), and renal insufficiency (serum creatinine  $\geq 200 \mu\text{mol/L}$ ) were recorded. Stroke was confirmed by clinical assessments and cranial Computerized Tomography (CT) scans. Assessment of known risk factors for stroke (hypertension, diabetes, hyperlipidemia, alcohol consumption, smoking, carotid atherosclerosis, and medication compliance) was also recorded. Long-term bedridden patients exhibiting no contraindications were treated with Low-Molecular-Weight Heparin (LMWH; 4,100 IU QD injection hypodermic), antiplatelet drugs (100 mg aspirin; 50 mg clopidogrel), and Renin-Angiotensin-Aldosterone System (RASS) blockers.

**Statistical analysis:** Data were analyzed by using the Statistical Package of Social Sciences (SPSS) version 16.0 for Windows, and the results were presented as the mean  $\pm$  standard deviation. Analysis of the differences between groups was performed by unpaired t-tests. Distributions between two groups were analyzed by Pearson Chi-Square ( $\chi^2$ ) tests, with Yates's corrections or Fisher's Exact tests applied when appropriate. A P value of  $<0.05$  was considered statistically significant. The risk factors of AF and stroke were analyzed by multivariable logistic regression with a p-value cut-off point of 0.15. Variables with  $P < 0.1$  by univariate analysis were included in the multivariate model, and P values  $< 0.05$  were considered significant.

## Results

A total of 587 rehabilitation patients were enrolled in the study (59% males, mean age 76.6 years), with long-term bedridden patients comprising a majority of the sample size (84.8%). During the three-year protocol, 54 cases of AF (9.2% of the total study population) were reported, and this subpopulation was composed of 40 cases with persistent AF (68.1% of the AF group) and 14 cases of paroxysmal AF (PAF; 31.9% of the AF group). Thirty-five AF patients presented with non-alvular heart diseases (64.8%), characterized by a Maximal Heart Rate (MHR) of  $78.3 \pm 15.3$  beats /min. Seventeen AF patients (31.5%) presented with a low heart rate (MHR  $<60$  beats /min). Four cases (7.4%) exhibited Sick Sinus Syndrome (SSS), and one case from this group received a permanent pacemaker implant and did not receive anti-arrhythmic drugs. The average disease course was  $20.8 \pm 13.6$  years.

Active management of AF in the elderly patients was done primarily through drug therapies (with one exception, as noted above). Of the 35 cases of AF with fast ventricular rate, 26 cases (70.3%) were treated by cedilanid, 5 cases (13.5%) were prescribed by amiodarone, and 4 cases (10.8%) received propafenone. Patients that did not present with SSS or high grade Atrio-Ventricular Block (AVB) received the following therapeutic strategies to control the ventricular rate: 24 patients (68.6%) were treated by digoxin; 9 patients (25.7%) were treated by metoprolol; and 2 patients (5.7%) were treated by

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diltiazem. Seven patients presenting with Paroxysmal Atrial Fibrillation (PAF; 50% of the AF patients with fast ventricular rate) were treated with amiodarone and propafenone cardioversion therapy. Two cases (28.9% of AF patients with fast ventricular rate) presented with a transient SSS and / or

high grade AVB performance. For the 12 patients with paroxysmal AF and no contraindications, 10 cases (83.3%) received a long-term treatment of metoprolol. The two cases with contraindications (16.7%) took diltiazem.

**Table 1.** Comparison of clinical presentations between atrial fibrillation patients (Group 1) and control patients (Group 2).

	Group 1 (n=54)	Group 2 (n=533)	P value
Age	78.5 ± 7.2	70.2 ± 11.9	0.002
Gender (female, (n%))	29 (53.7%)	214 (40.2%)	0.07
Hypertension (n, (n%))	22 (40.7%)	137 (25.7%)	0.001
Diabetes (n, (n%))	10 (18.5%)	32 (6.0%)	0.002
Hyperlipemia (n, (n%))	27 (50%)	238 (44.7%)	0.45
COPD (n, (n%))	10 (18.5%)	31 (5.8%)	0.001
CHF (n, (n%))	11 (20.4%)	41 (7.7%)	0.004
SHD (n, (n%))	4 (7.4%)	11 (2.1%)	0.06
Hypohepatia (n, (n%))	3 (5.6%)	12 (2.3%)	0.31
Renal inadequacy (n,(n%))	2 (8%)	7 (6.0%)	0.156
History of alcohol intake (n,(n%))	9 (16.7%)	42 (7.9%)	0.053
Smoking history (n,(n%))	10 (18.5%)	58 (10.9%)	0.148
MHR (beats/min)	78.3 ± 15.3	80.2 ± 13.7	0.09
LA diameter (mm)	38.2 ± 3.8	36.9 ± 2.9	0.047
Lvef (%)	60.6 ± 8.8	62 ± 6.6	0.414
LVEDD (mm)	48.6 ± 4	47.8 ± 2.6	0.246
Other arrhythmia (n,(n%))	6 (11.1%)	123 (23.7%)	0.04
Medicine (n,(n%))			
Renin-Angiotensin System (RAAS) blocker	10 (18.5%)	94 (17.6%)	0.87
Aspirin/Clopidogrel	38 (70.4%)	345 (64.7%)	0.41
Low Molecular Heparin	33 (61.1%)	367 (68.9%)	0.24
Warfarin	3 (5.6%)	8 (1.5%)	0.12
Statins	29 (53.7%)	257 (48.2%)	0.44

Number of subjects (n); percentage (%);COPD; CHF; SHD; MHR; minute (min); LA diameter; Milli-Metre (mm); LVEF; LEVDD; RASS; mean plus or minus the standard deviation (x ± y).

One of the goals of this study was to investigate the risk factors of AF in this unique elderly population. A multivariable logistic regression was performed to assess the association between AF and age, gender, hypertension, diabetes, COPD, CHF, LA diameter, warfarin treatment, alcohol consumption, liver dysfunction, smoking and other factors. Patients with AF (Group 1; N=54) were compared to the control population that did not present with AF (Group 2; N=533). Gender did not have an effect in the incidence of AF (Table 1). Age, hypertension, diabetes, COPD, CHF, LA diameter were significantly higher in Group 1 than those of the control group (P<0.05). Except for atrial arrhythmias, the control population

demonstrated a higher number of incidences of other types of arrhythmias than AF patients in Group 1 (P=0.04). No significant differences were observed between the two groups with regards to hyperlipidemia, Structural Heart Disease (SHD), smoking, alcohol consumption, liver and kidney dysfunction, MHR, LVEF, or (LEVDD; P>0.05, respectively). Our results show that age, hypertension, diabetes, COPD, LA diameter and CHF were associated with AF (P<0.05).

The variation of patient age, female gender, hypertension, diabetes, SHD, COPD, CHF, LA diameter, MHR, alcohol consumption, smoking, other types of arrhythmias, and warfarin treatment was analyzed by a bivariate regression

analysis. Age, hypertension and CHF were found to be independent predictors of AF in elderly patients receiving treatments at a rehabilitation center. The results of this analysis were as follows: age (Odds Ratio (OR)=2.232; 95% Confidence Interval (CI); Relative Risk (RR) ranging from 1.766 to 4.307; P=0.035), hypertension (OR=2.125; 95% CI; RR ranging from 1.410 to 3.921, P=0.021), and CHF (OR=1.886; 95% CI; ranging from 1.146 to 3.104; P=0.013). The secondary goal of this study was to investigate the risk factors of stroke in elderly rehabilitation patients. Multivariable logistic regression was performed to assess the association between stroke and the factors previously described. Patients presenting with stroke (Group 3; N=49 or 8.3% of the total study population) were compared to the control population of non-stroke patients (Group 4; N=538).

**Table 2.** Comparison of clinical presentations between stroke patients (Group 3) and control patients (Group 4).

	Group (n=49)	3 Group (n=538)	4 P value
Auricular fibrillation ( n,(n%))	13 (24.1%)	41 (7.6%)	<0.001
Age	75.1±8.9	73.4±9.9	0.034
Gender (female, (n%))	30 (61.2%)	213 (39.6%)	0.003
Hypertension (n, (n%))	20 (40.8%)	139 (25.8%)	0.024
Hyperlipemia (n, (n%))	33 (67.3%)	232 (43.1%)	0.001
Diabetes (n, (n%))	6 (12.2%)	36 (6.7%)	0.25
COPD (n, (n%))	6 (12.2%)	37 (6.9%)	0.79
CHF (n, (n%))	7 (14.3%)	45 (8.4%)	0.16
SHD (n, (n%))	4 (16.4%)	11 (2.1%)	0.03
Carotid atherosclerosis (n,(n%))	47 (95.9%)	493 (91.6%)	0.43
History of alcohol intake (n,(n%))	7 (14.3%)	44 (8.2%)	0.15
Smoking history (n, (n%))	11 (22.5%)	57 (10.6%)	0.013
Medicine (n, (n%))			
RAAS blocker	11 (22.4%)	93 (17.3%)	0.36
Aspirin/clopidogrel	33 (70.4%)	350 (64.7%)	0.75
Low molecular heparin	30 (61.2%)	370 (68.8%)	0.28
Warfarin	3 (6.1%)	8 (1.5%)	0.047
Statins	31 (63.2%)	255 (47.4%)	0.03

Out of 49 stroke cases in Group 3, 11 patients (22.4%) experienced one episode of stroke during hospitalization and two cases (4.1%) had multiple courses of stroke. Ischemic stroke presented in 44 cases (89.7%). Of the ischemic stroke cases, three patients (6.1%) presented with transient ischemic attack, and two patients presented as hemorrhagic stroke (4.1%). Analysis of the brain regions damaged during ischemic stroke found that 32 cases (65.3%) presented with multiple lesions of lacunar infarction, seven cases (14.3%) presented with damage to a single lobe, and 10 cases (20.4%) showed

damage to two and more lobes. Female patients had a significantly higher incidence for stroke (P=0.003; Table 2). Age, AF, hypertension, hyperlipidemia, SHD, smoking, and treatment with warfarin or statins were associated with stroke (P<0.05, respectively). There was no significant difference between stroke patients in Group 3 compared to the control population (Group 4) for comorbidities such as diabetes, COPD, CHF, alcohol consumption, or the administration of other drugs (P>0.05). The bivariate regression analysis demonstrated that hypertension (OR=1.667; 95% CI; RR ranging from 1.102 to 2.822; P=0.029) and AF (OR=2.926; 95% CI; RR ranging from 2.316 to 5.967; P<0.01) were independent predictors of stroke in this sample population.

## Discussion

Several large-scale epidemiological studies have shown that the total prevalence of AF in the elderly population (>60 years old) can be as high as 5.9%. AF results in nearly one third of all ischemic stroke cases, and non-valvular AF accounts for more than half of all cardiogenic stroke cases [6-10]. As the global population ages, the patient population in rehabilitation centers is increasing along with the prevalence of age-related disorders such as Alzheimer's disease and other cardiovascular diseases. Because the elder are particularly risky for AF and stroke, investigating the incidence and risk factors of these diseases is important for an early prevention and lowering mortality and morbidity. By examining an elderly population from a rehabilitation center (average age 76.6 ± 9.3 years old), we found the incidence of AF was 9.2%, and these patients presented with both non-valvular heart disease (64.8%) and persistent AF (68.1%).

A recent meta-analysis of AF patients demonstrated that age, female gender, hypertension, heart failure, diabetes, and coronary heart disease were clear risk factors. Other potential risk factors reported in the study included high body mass index, hyperthyroidism, alcohol consumption, chronic renal insufficiency, COPD, and smoking. Our results agree with these data, showing that age (OR=2.232, P=0.035), hypertension (OR=2.125, P=0.021), and CHF (OR=1.886, P=0.013) are independent risk factors for AF in elderly patients (Table 1). Although the relationship between age and AF has been confirmed by other studies [6-8], results of our study show that age is a primary risk factor in addition to hypertension in older subjects. Degenerative changes in the physiology of the heart may contribute to AF in the elderly. We observed an indirect line of evidence for these pathological changes in this current study, with 31.5% of patients presenting with slow AF and 7.4% of patients presenting with SSS. Hypertension can damage the left ventricular diastolic function and activate RAAS, which induces the enhancement of atrial pressure, atrial enlargement and fibrosis [11]. Increased atrial pressure is often associated with heart failure and results in atrial dilatation, a shorten period of atrial refractory, abnormalities in conduction velocity, and increased dispersion of repolarization. These pathological changes can account for

AF [12,13], since these factors either separately or jointly promote atrial fibrosis.

Elderly patients are particularly vulnerable to the vicious cycle of atrial anatomy: electrical remodeling that sustains AF. We found a significant increase in the larger left atrial (LA) diameter ( $38.2 \pm 3.8\text{mm}$ ) in Group 1 patients with AF compared to the control group ( $P=0.047$ ). However, our logistic regression analysis showed that LA diameter is not an independent risk factor for AF or predictive of its occurrence. In addition to the interaction among risk factors for AF, there is also a possibility that electrical remodeling may occur before anatomical reconstruction or during the accumulation of this reconstruction. Previous studies have shown that the conversion from paroxysmal AF to persistent AF can be sudden and discrete in most patients, rather than gradual as previously hypothesized [14]. Substantial AF burden surge has not been observed immediately before the transition point, which indicates that a single arrhythmia or a low degree abnormal rhythm may induce this persistent AF, and can be retained by a remodeled substrate [14].

Research indicates that age, hypertension, AF, diabetes, dyslipidemia, smoking, alcohol consumption, and physical inactivity are major risk factors for stroke [15]. In our current study, the prevalence of stroke was 8.3%, and AF patients contributed 24.1% of this population. We found that 89.7% of all stroke patients induced by AF presented with ischemic stroke. Some of the contributing factors leading to ischemic stroke may have included systolic dysfunction of damaged atrial myocardium leading to blood stasis, which could form a thrombosis in the left atrial auricle. The deciduous thrombosis would easily cause ischemic stroke if present. Since atherosclerosis of the large blood vessels can also be a contributing factor to ischemic stroke, elderly patients prone to developing peripheral atherosclerotic plaques are especially vulnerable. Although 7.6% of patients without AF suffered from stroke in our study, AF significantly increased the risk of stroke ( $P<0.01$ ) and supported previous observations [9].

Patients diagnosed with hypertension ( $N=159$ ; 27.1%) were at an increased risk of stroke in the current study ( $P=0.029$ ). The sustained high pressure within the blood vessels of hypertensive patients leads to the formation of atherosclerotic plaques and damages the vascular endothelial layer. A recent study found that a decrease of 10 mm Hg in Systolic Blood Pressure (SBP) was associated with approximately 30% lower risk of stroke in patients with the age between 60 and 79 years old [16]. Therefore, we screened our study population for hypertension to manage blood pressure levels and prevent stroke. We found the association between age, hyperlipidemia, structural heart disease, and smoking was higher in stroke patients (Group 3) compared to controls ( $P<0.05$ ), as others have previously observed [15]. However, logistic regression analysis did not indicate that these variables were predictive risk factors for stroke in our study. In addition to the contributions of ethnicity, the administration of warfarin and statin to stroke patients in our study may account for our observations. Administration of low molecular weight heparin

to long-term bedridden patients may also have had a protective effect [17,18].

Treatment of AF usually involves cardioversion to normal sinus rhythm or controlling the rate of ventricular rhythm, and maintenance is often achieved through the long-term administration of anticoagulant drugs. Recently, the control of ventricular rhythm was proposed as a first-line treatment strategy, especially in elderly patients with persistent AF who can tolerate the symptoms of AF. For these patients, ventricular rhythm control produced similar results as maintenance of sinus rhythm [17,19].

The characteristics of the population in this study were advanced age, heart failure (20.4%) and persistent AF (68.1%). Of the 37 patients with fast-ventricular rhythm, the vast majority (70.3%) controlled ventricular rhythm by cedilanid and chose digoxin for long-term maintenance (68.6%). Digoxin controls ventricular rhythm successfully when activity levels are low and benefited the bedridden patients in this study. A total of 25.7 percent of patients selected metoprolol, and the majority of patients with paroxysmal AF (83.3%) chose long term administration of metoprolol. We found that cardioversion should be applied cautiously to patients with paroxysmal AF, since two out of seven cases suffered from a severe transient block of the conduction system during cardioversion. In addition, 18.5% of patients with paroxysmal AF took RAAS blockers, based on the recent evidence that RAAS blockers and  $\beta$ -blockers can reverse atrial remodeling [20,21]. According to risk score proposed in the 2010 ESC AF guidelines, the majority of patients with AF in this study needed warfarin. However, considering the risk of bleeding and poor compliance, only 5.6% of the AF patients took warfarin. Most of patients chose small doses of low molecular weight heparin, aspirin or clopidogrel as alternative treatments.

There were limitations to our study, such as patient histories being indirectly collected from family members and potentially affecting the objectivity. Second, patient noncompliance during examination could affect the reliability of the clinical assessments. Furthermore, additional analysis regarding incompatible drug interactions was not performed. In conclusion, our study confirmed that there is a higher risk of stroke and AF in elderly patients undergoing rehabilitation. Controllable risk factors such as hypertension, CHF and AF can be actively managed to reduce the reoccurrence of AF or the potential for stroke.

## **Conclusion**

Geriatric patients present a unique population of challenges for health care providers in rehabilitation centers. In addition to a poor nutritional status and a reduced physical mobility, age-associated factors such as comorbidities may predispose older patients to AF and stroke. In this work, we examined the prevalence of AF and stroke in elderly patients admitted to multiple healthcare facilities, but less is known about the risk factors associated with AF and stroke specifically within rehabilitation centers. The present study examined 587 elderly

patients admitted to a rehabilitation center in Ningbo, China, and analyzed the risk factors, clinical presentations of AF and stroke events, as well as treatments of this unique population.

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### \*Correspondence to

Hui-min Chu

Department of Cardiology

Ningbo No.1 Hospital Affiliated to Zhejiang University

PR China